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54 **Seamless soft capsule.**

57 A soft capsule composed of a plurality of cells
 coalesced to each other and filling substances en-
 capsulated in the individual cells, the wall of at least
 one of the cells being formed of a material different
 from a material forming the wall of at least one of the
 other cells, and said capsule being seamless. The
 soft capsule can be produced by

(a) preparing a plurality of composite jet
 streams each consisting of a stream of a film-for-
 ming liquid substance for forming a cell wall and
 within said stream of a film-forming liquid substance
 a single stream, or a plurality of independent
 streams, of a filling substance having flowability, the
 film-forming liquid substance in at least one of the

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composite jet streams being different from the film-forming liquid substance in at least one of the other composite jet streams,

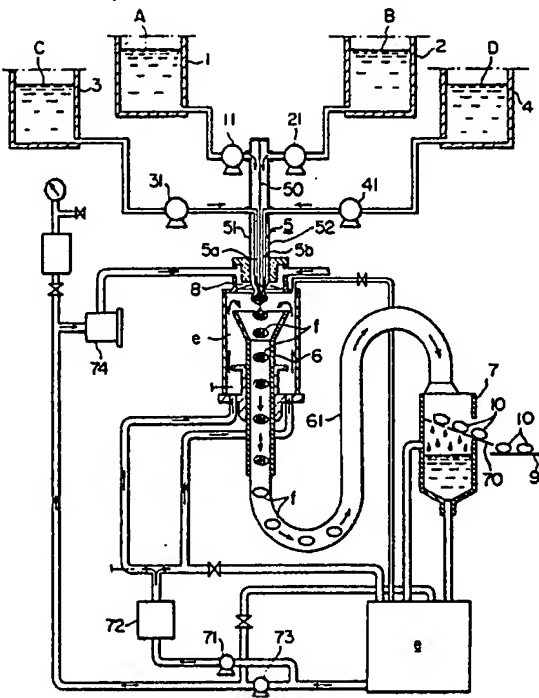
(b) advancing the plurality of composite jet streams in closely spaced relationship into and through a stream of a liquid medium substantially incapable of dissolving the film-forming liquid substance in the flowing direction of the liquid medium stream,

(c) coalescing the adjacent composite jet streams to each other to form a single composite jet stream in the liquid medium stream,

(d) cutting the single composite jet stream to a predetermined length successively from its leading end in the liquid medium stream, and

(e) solidifying the cell walls of the resulting soft capsule.

Fig. 1



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This invention relates to a seamless soft capsule, and more specifically, to a seamless soft capsule having a multicellular structure, and a method of its production.

A multicellular soft capsule having its inside partitioned by a film was recently proposed (see Japanese Laid-Open Patent Publication No. 109520/1985). This patent document states that the multicellular soft capsule is obtained by partitioning a soft capsule shell composed of an upper film and a lower film into two cells by means of a partitioning film, and filling different drugs into the two cells. As a result, two drugs which are not desired to be mixed can be stably included in a single soft capsule. By using materials having different solubilities and dissolving speeds, it is possible to cause one part of a single capsule to be released and absorbed in the stomach and the other part, in the intestines. It is also possible to make one part of the capsule fast-releasing and the other part slow-releasing.

Since the proposed multicellular soft capsule is produced by a rotary method or a flat plate method, the capsule shell has seams. Hence, in spite of the aforesaid advantages, it has the defect that the filled drugs leak from the seams, or air comes through the seams to deteriorate the contents oxidatively. Furthermore, by the rotary method or the flat plate method, it is difficult to produce multicellular soft capsules having a small size, and moreover, the cost of production becomes high. Furthermore, since both surfaces of the partitioning film in the aforesaid multicellular soft capsule are formed of the same material, if a drug to be filled in one of the cells reacts with the components of the partitioning film, it cannot be included in such a capsule.

It is an object of this invention to provide a multicellular seamless soft capsule free from the aforesaid defects.

Another object of this invention is to provide a simple and inexpensive method of producing the aforesaid seamless soft capsule, which can easily give capsules of a small size as well.

Further objects and advantages of this invention will become apparent from the following detailed description.

According to one aspect of this invention, there is provided a soft capsule composed of a plurality of cells coalesced to each other and filling substances encapsulated in the individual cells, the wall of at least one of the cells being formed of a material different from a material forming the wall of at least one of the other cells, and said capsule being seamless.

According to another aspect of this invention, the seamless soft capsule of this invention is produced by a method which comprises

(a) preparing a plurality of composite jet streams each consisting of a stream of a film-forming liquid substance for forming a cell wall and within said stream of a film-forming liquid substance a single stream, or a plurality of independent streams, of a filling substance having flowability, the film-forming liquid substance in at least one of the composite jet streams being different from the film-forming liquid substance in at least one of the other composite jet streams,

(b) advancing the plurality of composite jet streams in closely spaced relationship into and through a stream of a liquid medium substantially incapable of dissolving the film-forming liquid substance in the flowing direction of the liquid medium stream,

(c) coalescing the adjacent composite jet streams to each other to form a single composite jet stream in the liquid medium stream,

(d) cutting the single composite jet stream to a predetermined length successively from its leading end in the liquid medium stream, and

(e) solidifying the cell walls of the resulting soft capsule.

The capsule and the method of producing it in accordance with this invention will be specifically described with reference to the accompanying drawings in which:

Figure 1 is a systematic view, partly in section, of one example of an apparatus used to practice the method of this invention in its entirety;

Figure 2 is an enlarged end view of a composite nozzle in the apparatus shown in Figure 1;

Figure 3 is an enlarged sectional view of a seamless soft capsule produced in accordance with this invention by the apparatus of Figure 1;

Figure 4 is an end view showing another example of the composite nozzle;

Figure 5 is a sectional view of a seamless soft capsule produced by using the composite nozzle of Figure 4;

Figure 6 is an end view of still another example of the composite nozzle;

Figure 7 is a sectional view of a seamless soft capsule produced by using the composite nozzle of Figure 6;

Figure 8 is an end view of yet another example of the composite nozzle;

Figure 9 is a sectional view of a seamless soft capsule produced by using the composite nozzle of Figure 8;

Figure 10 is an end view of a further example of the composite nozzle;

Figure 11 is a sectional view of a soft capsule produced by using the composite nozzle of Figure 10; and

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Figure 12 is an enlarged sectional view of the principal parts of a still further example of the composite nozzle.

In Figure 1, the reference numeral 1 represents a tank holding a film-forming liquid substance A for forming a cell wall; 2, a tank holding a film-forming substance B which is different from the substance A; 3, a tank holding a filling substance C; and 4, a tank holding another filling substance D. The tanks 1, 2, 3 and 4 are individually provided with heating means (not shown) for maintaining the substances A, B, C and D at suitable temperatures for maintaining them flowable. The substances A, B, C and D are supplied to the tanks 1, 2, 3 and 4 respectively. Metering pumps 11, 21, 31 and 41 are provided for feeding the substances A, B, C and D of the tanks 1, 2, 3 and 4 to a composite nozzle 5. The composite nozzle 5, as shown in Figures 1 and 2, is a duplex nozzle consisting of outside nozzles 51 and 52 having a semielliptical cross sectional shape resulting from partitioning an elliptical tube by a partitioning wall 50 at its center and inside nozzles 5a and 5b of a smaller diameter disposed nearly centrally in the outside nozzles 51 and 52 respectively. The outside nozzles 51 and 52 communicate with the tanks 1 and 2, and the inside nozzles 5a and 5b, with the tanks 3 and 4. The composite nozzle 5 faces downwardly along a downwardly flowing stream of a liquid medium g within a capsule-forming tank 6.

The specification of the composite nozzle 5 may be freely changed according, for example, to the use of the capsule to be produced. For example, for use in making a capsule used as a medicine, a typical specification is that in Figure 2, the elliptical tube has an outside long diameter d_L of 5 to 20 mm and an outside short diameter d_s of 3 to 12 mm, and the inside nozzles have an outside diameter of d_i of 2 to 9 mm, and the individual tubes have a thickness of 0.1 to 2 mm.

The liquid medium g formed, for example, of liquid paraffin is sent to a heat exchanger 72 from a recovery hopper 7 concurrently acting as a storage tank by means of a pump 71. In the heat exchanger 72, it is cooled to a moderate temperature of, for example, about 5°C and supplied to the upper portion of the capsule-forming tank 6. It becomes a downwardly flowing stream within the capsule-forming tank 6, and is circulated to the recovery hopper 7 via a capsule recovery tube 61. A part of the liquid medium g is supplied to a pulse stream-forming device 74 by means of a pump 73 from the hopper 7. It is converted to a regular pulse stream in the pulse stream-forming device 74 and supplied to a pulse stream nozzle 8 provided within the capsule-forming tank 6.

The pulse stream nozzle 8 is a circular nozzle provided immediately below, and coaxially with, the composite nozzle 5 and having a slightly larger diameter than the diameter of the elliptical tube of the composite nozzle 5. A pulsating stream of the liquid medium g from the nozzle 8 is extruded toward the center of the nozzle 8 from an annular slit formed within the nozzle 8 in such a manner as to surround a single composite jet stream formed by the composite nozzle 5.

Film-forming liquid substances A and B for cell wall formation and filling substances C and D to be filled in a capsule are sent under pressure to nozzles 51, 52, 5a and 5b constituting the composite nozzle 5 by means of the metering pumps 11, 21, 31 and 41. From the nozzle 51, a composite jet stream composed of a stream of the film-forming substance A and a single stream of the filling substance C is extruded into, and along, the downwardly flowing liquid medium flow within the capsule-forming tank 6, and from the nozzle 52, a composite jet stream composed of a stream of the film-forming substance B and a stream of the filling substance D is likewise extruded into, and along, the downwardly flowing liquid medium stream within the capsule-forming tank 6. Since the nozzles 51 and 52 form an integral unit via a partitioning wall 50, the two composite jet streams extruded as above, nearly simultaneously with their formation, are coalesced to each other into a single composite jet stream within the downwardly flowing stream of the liquid medium g owing to the surface tensions of the film-forming liquid substances A and B.

The speeds of extruding the composite jet streams, and the flow rate of the downwardly flowing stream of the liquid medium g can be varied depending upon, for example, the types of the film-forming liquid substances forming the composite jet streams, the type of the liquid medium g and the size of the composite nozzle, and any skilled person in the art would be able to determine optimum conditions easily by routine experiments. As tentative standards, it is convenient to adjust the extruding speed of each composite jet stream to about 4 to 40 m/min., and the flow rate of the downwardly flowing liquid medium stream to about 5 to 50 m/min.

The single composite jet stream so formed undergoes impact of the regular pulse stream of the liquid medium g from the pulse stream nozzle 8, whereby as shown in Figure 1, necks or narrowed parts are formed at certain intervals beginning with its leading end. The jet stream is drawn downwardly by the downwardly flowing stream of the liquid medium g ; and successively cut off at the neck portions by the downwardly drawing force. Each cut droplet f contains the filling substances C

and D encapsulated in the film-forming liquid substances A and B by the surface tension of the substances A and B, and is formed into a seamless capsule, which is roundish as a whole, while moving down through the downwardly flowing stream of the liquid medium g. The capsules formed advance to the hopper 7 via the recovery tube 6l while being cooled and solidified. In the hopper 7, the capsules are separated from the liquid medium g by a separator 70, supplied to a conveyor 9 provided on one side of the separator 70, and sent to a drying step where they are dried to produce a final product.

By the method described above, there are obtained unitary seamless soft capsules 10 in which a cell a formed of the film-forming substance A and the filling substance C encapsulated in it is coalesced to a cell b formed of the film-forming substance B which is different from the substance A and the filling substance D encapsulated in it, and the cell wall is of a double structure at the coalesced part, as shown in Figure 3.

The film-forming substance for cell formation may be any material which can be formed into a thin film from its melt or solution, and after film formation can be solidified by cooling and/or drying. Substances usually employed in forming the shell of a soft capsule may be used in this invention. Examples include film-forming substances composed of gelatin or gelatin derivatives such as succinic gelatin and incorporated therein, plasticizers [such as glycerol, sorbitol, propylene glycol and Carbowax (polyethylene glycol)], essences and flavors (such as peppermint oil, cinnamon oil and strawberry), dyes (such as yellow No. 4, yellow No. 5, red No. 1, blue No. 1 and copper chlorophyllin), opacifying agents (such as titanium dioxide and red iron oxide), solubility controlling agents (such as cellulose acetate phthalate, alkali metal salts of hydroxypropylmethyl cellulose, alkali metal salts of hydroxymethyl cellulose acetate succinate, alkali metal salts of alginic acid, alkali metal salts of polyacrylic acid, methyl cellulose, carboxymethyl cellulose, casein, collagen, agar powder, polyvinyl alcohol and pectin), etc. selected as desired. It is generally used as a liquid by dissolving it in water under heat.

The filling substance to be encapsulated in each cell of the soft capsule of this invention can be any drug which does not dissolve the cell wall nor react with the components of the cell wall. It is preferably liquid when it is to be filled in the cell in accordance with the method of this invention. Accordingly, when the drug is a solid, it is desirably filled in a flowable state as a solution, emulsion or suspension.

According to the method of this invention, by using a combination of two or more suitable film-forming substances selected from those exemplified above, at least one of a plurality of cells constituting the resulting soft capsule can have a different dissolving time in the digestive tract from at least one of the other cells (for example, whether fast-releasing or slow-releasing), or at least one cell may have different dissolving characteristic from at least one of the other cells (for example, whether released and adsorbed in the stomach or the intestines).

Furthermore, in the present invention, the filling substances to be encapsulated in the cells may be varied from cell to cell. As a result, a single capsule may be obtained in which a drug expected to be fast-acting is filled in a fast-dissolving cell and a drug desired to be slow-acting is filled in a slow-dissolving cell. Alternatively, a single capsule cell may be obtained in which a drug expected to develop its effect in the stomach is filled in a cell soluble at the stomach, and another drug expected to develop its effect in the intestines is filled in a cell soluble at the intestines.

The shape of the soft capsule 10 can be selected by changing the shape of the end surface of the composite nozzle 5 on the extrusion side. Some modified examples of the composite nozzle 5 will be described below.

The composite nozzle 5 shown in Figure 4 is composed of duplex outside nozzles 5l and 52 having a cocoon-shaped cross section and smaller-diameter inside nozzles 5a and 5b disposed coaxially within the outside nozzles 5l and 52 respectively. The capsule 10 obtained by using this composite nozzle 5 has a cocoon-shaped cross-section as shown in Figure 5. It is a seamless soft capsule in which filling substances c and d are independently encapsulated in cells a and b.

Figures 6 and 8 show other examples of the composite nozzle 5. These nozzles 5 are each divided into three outside nozzles 5l, 52 and 53 by two or three partitioning walls 50 and smaller-diameter inside nozzles 5a, 5b and 5c are disposed centrally in the outside nozzles 5l, 52 and 53 respectively. By simultaneously extruding different film-forming substances from the outside nozzles 5l, 52 and 53 and filling substances from the inside nozzles 5a, 5b and 5c with the use of these composite nozzles 5, there can be produced seamless soft capsules 10 in which the filling substances c, d and h are encapsulated in the cells a, b and g formed from cell walls of different materials, as shown in Figures 7 and 9.

Figure 10 shows still another example of the composite nozzle 5 in which a large-diameter tube of an elliptical cross-sectional shape is divided into a large-diameter outside nozzle 5l and a small-

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diameter outside nozzle 52 by a partitioning wall 50 at a site about 1/3 as viewed from one end surface of the tube, inside nozzles 5a and 5b having a smaller diameter are disposed in the large-diameter outside nozzle 51 in spaced-apart relationship, and an inside nozzle 5c having a smaller diameter is disposed centrally in the small-diameter outside nozzle 52.

When the composite nozzle 5 shown in Figure 10 is used, different film-forming substances and different filling substances are simultaneously extruded along the stream of the liquid medium in the apparatus shown in Figure 1 from the outside nozzles 51 and 52, and the inside nozzles 5a, 5b and 5c, respectively. Thus, a composite jet stream containing two independent streams of the filling substances c and h and a composite jet stream containing one stream of the filling substance b are formed simultaneously in the capsule-forming tank 6 as in Figure 1, and coalesced into a single composite jet stream. The single composite jet stream is successively cut in a predetermined size from its leading end in the flowing direction by the action of the pulsating flow of the liquid medium.

The soft capsule 10 produced in this way is a seamless soft capsule composed of a unitary structure of a cell a and two filling substances c and h independently encapsulated in it and a cell b and one filling substance d encapsulated in it, as shown in Figure 11.

The soft capsule 10 shown in Figure 11 and the method of production using the composite nozzle shown in Figure 10 give a capsule in which two filling substances c and h are independently encapsulated in a cell having a cell wall of the same material. Hence, they are beneficial when different drugs which are to be released simultaneously from one cell a but should not be mixed beforehand are used as the filling substances c and h.

Even when the outside nozzles 51 and 52 of the composite nozzle 5 are not unitary but are slightly spaced from each other as shown in the embodiment given in Figure 12, composite jet streams extruded separately from the nozzles 51 and 52 are coalesced into a single composite jet stream by the pulsating flow of the liquid medium, and cut to a predetermined length from its leading end in the flowing direction. Hence, the method of this invention can be practiced in the same way by using the composite nozzle 5 shown in Figure 12.

The single composite jet stream formed along the flow of the liquid medium g may be cut to a predetermined length from its leading end in the flowing direction by intermittently increasing the speed of the downwardly flowing stream of the liquid medium g, and intermittently pulling off the composite jet stream downwardly by the quickened downwardly flowing liquid stream, instead of apply-

ing a pulsating flow of the liquid medium g sideways to the composite jet stream in the embodiments described above. By this alternative procedure, too, the single composite jet stream can be cut successively to a predetermined length.

According to this invention, one capsule contains a plurality of cells whose cell walls are made of different materials. Hence, the present invention is suitable for filling both a substance to be released and absorbed in the stomach and a substance to be released and absorbed in the intestines, or at least two substances having different dissolving times, in a separated state in a single capsule. Since the soft capsule of the invention is seamless, the filled substances can be retained stably while preventing their deterioration by oxidation or otherwise. According to the method of this invention, capsules of any desired sizes can be produced, and capsules having a smaller size than in the prior art can be easily produced at low cost.

The following Example illustrates the present invention more specifically.

EXAMPLE I

Referring to Figure 1, a film-forming substance A was filled in tank 1, and a film-forming substance B, in tank 2. These film-forming substances A and B were extruded from composite nozzle 5 having a outside long diameter (d_L) of 13 mm, an outside short diameter (d_s) of 9 mm and a thickness of 1 mm (Figure 2) by metering pumps 11 and 21. The amount of each of the film-forming substances A and B was 65.7 g/min.

In the meantime, a filling substance C was filled in tank 3, and another filling substance D, in tank 4. The filling substances C and D were extruded from nozzles 5a and 5b having an outside diameter (d_i) of 3 mm, an inside diameter of 2 mm and a thickness of 0.5 mm (Figure 2) by metering pumps 31 and 41. The amount of each of the filling substances extruded was 36 g/min. Composite jet streams composed of the film-forming substances A and B and the filling substances C and D flowed at a rate of 10 meters/min.

A paraffin oil as a cooling medium g within vessel 7 and heat-exchanger 72 was maintained at 3°C, and flowed downwardly in capsule-forming tank 6 at a flow rate of 15 m/min. A pulsating flow of the paraffin oil generated from pulse flow generator 74 was extruded at equal time intervals from pulse flow nozzle 8 accurately 15 times per second.

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Within the capsule-forming tank, capsules were formed at a rate of 15 per second at intervals of about 11 mm. After drying, each of the capsules had a long diameter of 8 mm and a short diameter of 6 mm, and the amount of each of the filling substances was 40 mg per capsule.

The film-forming substance A is a solution consisting of 20 parts of gelatin, 5 parts by weight of glycerol, 8 parts by weight of sorbitol and 67 parts by weight of purified water which was maintained at about 60°C.

The film-forming substance B was a solution consisting of 18 parts by weight of gelatin, 5 parts by weight of glycerol, 2.5 parts by weight of sodium alginate and 74.5 parts by weight of purified water which was maintained at about 60°C.

The filling substances C and D were solutions composed of different drugs which were maintained at about 25°C.

By the above procedure, there was produced a seamless soft capsule 10 which contained a core c composed of the filling substance C encapsulated in a gastric-soluble film a composed of the film-forming substance A and a core d composed of the filling substance D encapsulated in an enteric-soluble film b independently from each other, with the film portion separating the core c from the core d being of a double structure.

When the resulting soft capsule 10 was immersed in the first solution (gastric juice) stipulated in the Revised Method of Testing Disintegration in accordance with Japanese Pharmacopoeia, the film a dissolved in several minutes to release the core c, whereas the film b did not dissolve for more than 2 hours.

When the soft capsule 10 was immersed in the second solution (intestinal fluid) in the Revised Method of Testing Disintegration in accordance with Japanese Pharmacopoeia, both the films a and b dissolved within 2 to 3 minutes.

EXAMPLE 2

In the same way as in Example 1, film-forming substances A and B were extruded from a composite nozzle having an outside long diameter (D_L) of 7.5 mm, an outside short diameter (D_S) of 3.5 mm and a thickness of 0.5 mm. The amount of each of the film-forming substances A and B extruded was 21.9 g/min.

In the meantime, filling substances C and D were extruded extruded from nozzles 5a and 5b having an outside diameter (d_i) of 1 mm and a thickness of 0.1 mm. The amount of each of the substances C and D extruded was 18.6 g/min. The

speed of the composite jet stream at this time was 6 m/min. A paraffin oil was used as a cooling medium e and caused to flow in capsule-forming tank 6 at a rate of 22.5 m/min.

A pulsating flow of the paraffin oil generated from the pulse stream generator 74 was extruded from pulse stream nozzle 8 at equal time intervals accurately 50 times per second.

In capsule-forming tank 6, fifty capsules were formed per second at intervals of about 7.5 mm. After drying, each of the capsule had a long diameter of 3.5 mm and a short diameter of 2.5 mm. The amount of each of the filling substances C and D was about 6.2 mg.

Claims

1. A soft capsule composed of a plurality of cells coalesced to each other and filling substances encapsulated in the individual cells, the wall of at least one of the cells being formed of a material different from a material forming the wall of at least one of the other cells, and said capsule being seamless.

2. The soft capsule of claim 1 wherein at least one of the cells and at least one of the other cells are formed of cell wall materials having different dissolving times in the digestive tract or different dissolving characteristics in the digestive tract.

3. The soft capsule of claim 1 wherein the filling substance encapsulated in the plurality of cells are different from one another.

4. The soft capsule of claim 1 which is composed of 2 or 3 cells.

5. A method of producing the soft capsule of claim 1, which comprises

(a) preparing a plurality of composite jet streams each consisting of a stream of a film-forming liquid substance for forming a cell wall and within said stream of a film-forming liquid substance a single stream, or a plurality of independent streams, of a filling substance having flowability, the film-forming liquid substance in at least one of the composite jet streams being different from the film-forming liquid substance in at least one of the other composite jet streams.

(b) advancing the plurality of composite jet streams in closely spaced relationship into and through a stream of a liquid medium substantially incapable of dissolving the film-forming liquid substance in the flowing direction of the liquid medium stream,

(c) coalescing the adjacent composite jet streams to each other to form a single composite jet stream in the liquid medium stream,

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(d) cutting the single composite jet stream to a predetermined length successively from its leading end in the liquid medium stream, and

(e) solidifying the cell walls of the resulting soft capsule.

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6. The method of claim 5 wherein each of said plurality of composite jet streams is formed by using a composite nozzle comprised of an outside nozzle and at least one small-diameter inside nozzle disposed therein and simultaneously extruding the film-forming liquid substance from the outside nozzle and the filling substance from the inside nozzle.

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7. The method of claim 5 wherein the cutting of the single composite jet stream is carried out by intermittently applying a pulsating flow of a liquid medium from an annular slit surrounding the single composite jet stream.

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8. The method of claim 5 wherein the film-forming liquid substance in at least one of the plurality of composite jet streams has a different dissolving time in the digestive tract or a different dissolving characteristic in the digestive tract from the film-forming liquid substance in at least one of the other composite jet streams.

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9. The method of claim 5 wherein the plurality of composite jet streams contain different filling substances.

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Fig. 1

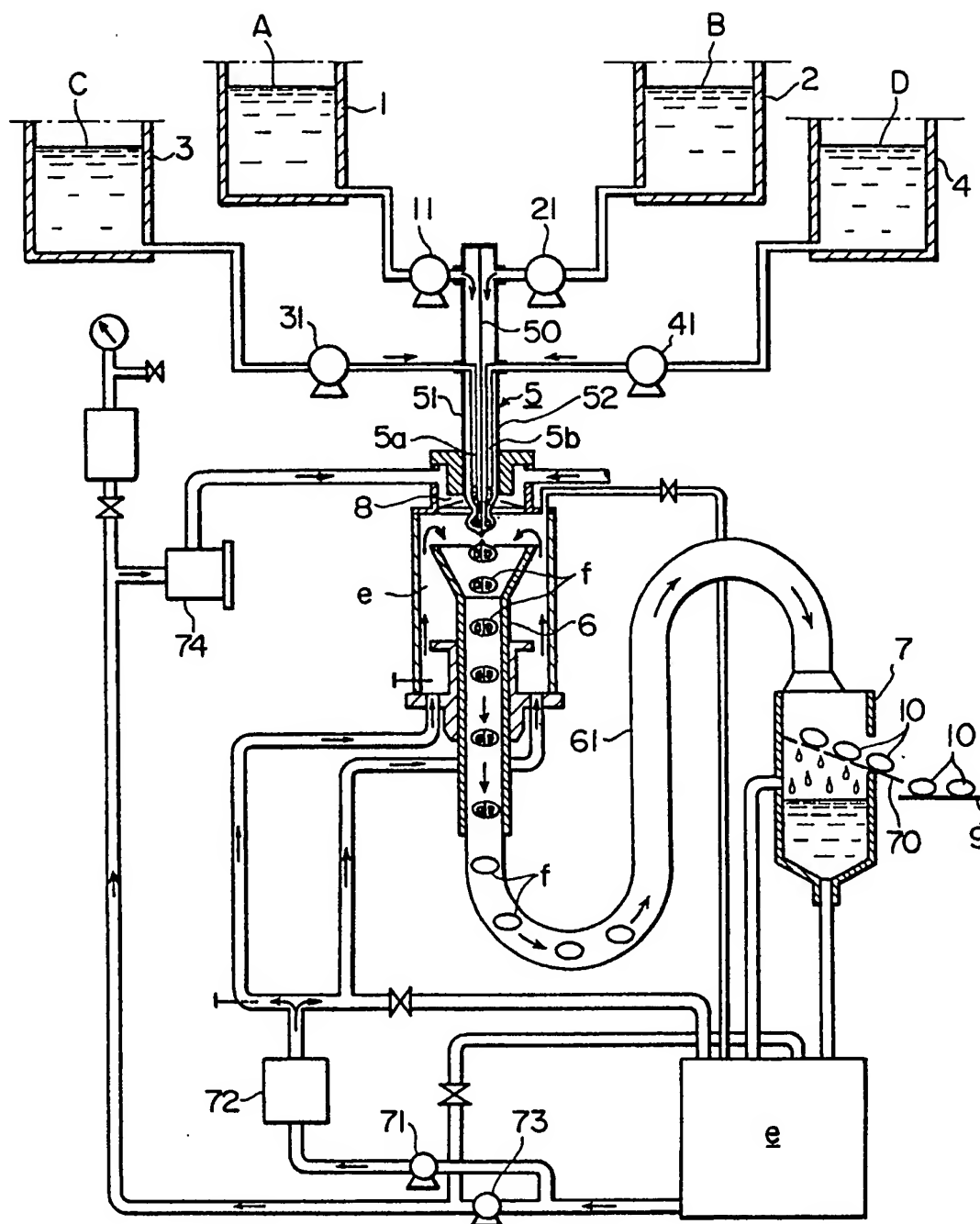


Fig. 2

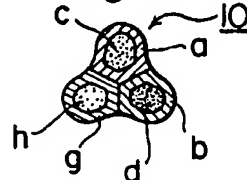


Fig. 4

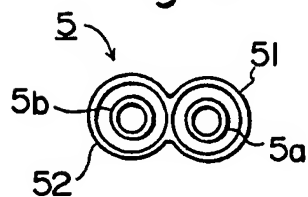


Fig. 10

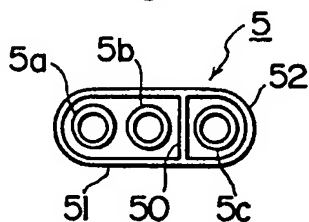


Fig. 5

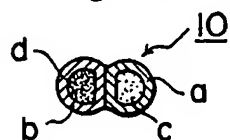


Fig. 11

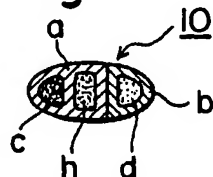
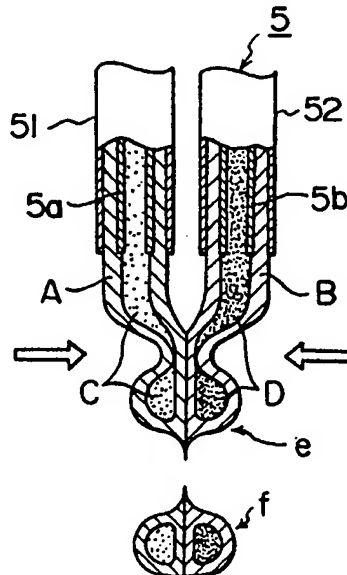


Fig. 12





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12 **EUROPEAN PATENT APPLICATION**

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43 Date of publication of application:
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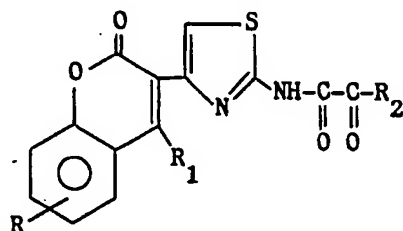
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54 **4-(3-coumarinyl)-thiazole-derivatives with anti-allergic, anti-anaphylactic and anti-arthritic activity and compositions containing them.**

57 Compounds of formula



(I)

(wherein R, R₁ and R₂ have the meanings reported in the specification)
 and their preparation are described.

The compounds of formula I have anti-allergic, anti-anaphylactic and anti-arthritic activity and are useful in pharmaceutical field.

Compositions for pharmaceutical use containing a compound of formula I as active ingredient are described too.

EP 0 284 017 A1

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4-(3-COUMARINYL)-THIAZOLE-DERIVATIVES WITH ANTI-ALLERGIC, ANTI-ANAPHYLACTIC AND ANTI-ARTHRITIC ACTIVITY AND COMPOSITIONS CONTAINING THEM

The present invention relates to compounds with anti-allergic, anti-anaphylactic and anti-arthritis activity and, more particularly, relates to derivatives of 2-thiazolyl-oxamic acid, their preparation and their use in pharmaceutical field.

The compound known as Cromolyn (Merck Index 10th Ed. no. 2580, page 371) or as disodium cromoglycate (described in U.K. Patent no. 1,144,906 - Fisons) has the characteristic of preventing the release of the autacoids formed during allergic reactions and induced by antigen-antibody interactions.

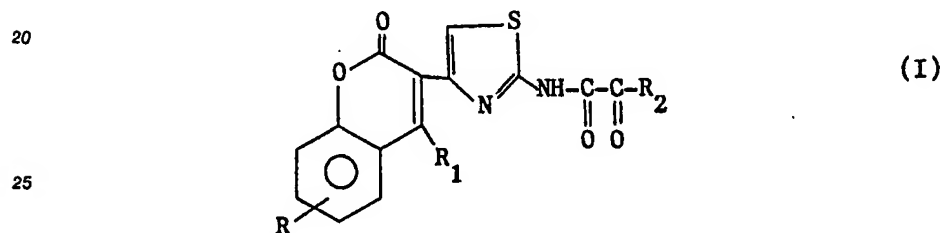
For this characteristic disodium cromoglycate is used in therapy as anti-allergic drug especially in asthmatic diseases.

However said compound is not absorbed after oral administration and this disadvantage limits its application considerably.

In order to attempt to overcome this disadvantage many other compounds were prepared which modified little by little the structure of disodium cromoglycate so that compounds structurally and chemically different from the parent compound were obtained.

Among these compounds the derivatives of phenyloxamic acid [J. Med. Chem., 21(9), 930, (1978)] and of 4-aryl-2-thiazolyl-oxamic acid (U.K. Patent Application no. 2,023,580 - Boehringer Ingelheim and European Patent no. 44442 - BASF) may be cited.

We have now found and they are the object of the present invention, compounds of formula

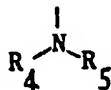


wherein

R and R₁, which are the same or different, represent hydroxy, a hydrogen or a halogen atom, a C₁-C₄ alkyl or alkoxy;

R₂ represents hydroxy, an OR₃ group or a

group;



R₃ represents a C₁-C₄ alkyl, a benzyl, a group of formula -(CH₂-CH₂-O)_n-R₄ wherein n represents an integer from 1 to 4 and R₄ represents a hydrogen atom or a C₁-C₄ alkyl;

R₄ and R₅, which are the same or different, represent a hydrogen atom, a C₁-C₄ alkyl, a benzyl, a phenyl, or R₄ and R₅, together with the nitrogen atom to which they are bonded, form a 1-piperidinyl, 1-piperazinyl, 4-methyl-1-piperazinyl radical.

Furthermore, object of the present invention are the salts of the compounds of formula I wherein R₂ represents hydroxy, with non-toxic organic or inorganic bases suitable for pharmaceutical use and the salts of the compounds of formula I wherein R₂ contains a basic function, with non-toxic organic or inorganic acids suitable for pharmaceutical use.

Specific examples of said bases are sodium, potassium or calcium hydroxide, methylamine, isopropylamine, hexylamine, diethylamine, ethanolamine, 2-hydroxymethyl-2-amino-1,3-propanediol, glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, arginine, lysine, cystine, cysteine, methionine, phenylalanine, tyrosine, tryptophan and histidine.

Examples of suitable acids are hydrochloric or hydrobromic acid, benzoic acid, 4-hydroxybenzoic acid,

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citric acid, tartaric acid and succinic acid.

If it is not otherwise specified, the radicals representing the meanings of the substituents in general formula I are preferably:

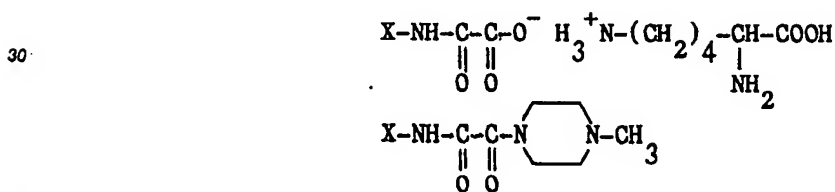
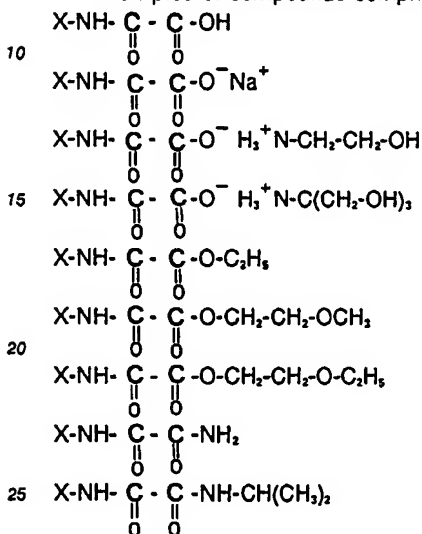
alkyl = linear or branched C₁-C₄ alkyl,

5 alkoxy = C₁-C₄ alkoxy,

alkoxycarbonyl = alkoxycarbonyl having from 1 to 4 carbon atoms in the alkoxy portion,

halogen = fluorine, chlorine, bromine or iodine atom.

Examples of compounds comprised in formula I are the followings:



wherein X represents the group



50 and wherein R and R₁ have the same above reported meanings but preferably they represent a hydrogen atom, a chlorine or bromine atom, hydroxy, a methoxy or ethoxy group.

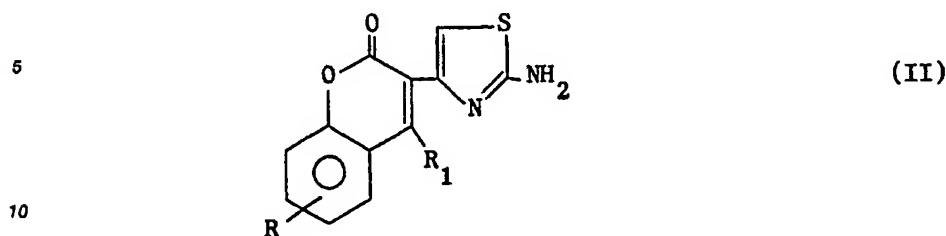
Preferred meanings of R₄ and R₅, the same or different, are hydrogen, methyl or ethyl or R₄ and R₅, together with the nitrogen atom to which they are bonded, are a 1-piperidiny, 1-piperaziny or 4-methyl-1-piperaziny radical.

55 The compounds of formula I are endowed with anti-allergic, anti-anaphylactic and anti-arthritis activity and they can be used in pharmaceutical field.

The preparation of the compounds of formula I is carried out by using methods already known in organic chemistry.

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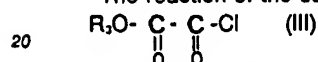
Useful starting materials are the compounds of formula



(wherein R and R₁ have the above reported meanings)

15 2-amino-4-(3-coumarinyl)-thiazoles of formula II are known compounds [C.F. Koelsch, J. Am. Chem. Soc. 72, 2993 (1950); M. Trkovnik et al., Org. Prep. and Proced. Int. 10, 215 (1978)] or they can be easily prepared from the corresponding 3-acetyl-coumarine (2H-1-benzopyran-2-one) by bromination and condensation of the so obtained alpha-bromo-ketone with thiourea.

The reaction of the compounds of formula II with derivatives of oxalic acid of formula



(wherein R₂ has the above reported meanings)

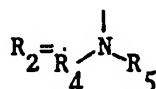
carried out in the presence of an organic or inorganic base and of a solvent that may be the organic base itself, gives the esters of formula I (R₂ = OR₃).

From these esters, the other compounds of formula I are prepared by means of known reactions.

25 For instance, the hydrolysis of the esters of formula I wherein R₂ = OR₃ gives the corresponding acids (R₂ = OH) which, if desired, can be salified by reaction with a pharmaceutically acceptable base.

The reaction of the compounds of formula I wherein R₂ = OR₃ with ammonia or with a suitable amine gives the compounds of formula I wherein R₂ = NH₂ or

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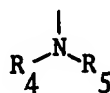
35 respectively.

Such compounds, in case they contain basic groups, can be salified, then, by reaction with a pharmaceutically acceptable acid. Other esters of formula I can be prepared by means of known methods from the acids as well as by transesterification.

40 The compounds object of the present invention have interesting anti-allergic, anti-anaphylactic and anti-arthritic properties.

The compounds of this invention are more active than known compounds such as disodium cromoglycate, however the anti-allergic and anti-anaphylactic activity is particularly remarkable in the compounds of formula I wherein R₂ is hydroxy or an OR₃ group. On the other hand the compounds of formula I wherein R₂ is a

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group are particularly preferred as far as their anti-arthritic activity is concerned.

Anti-allergic and anti-anaphylactic activity

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With reference to the anti-allergic and anti-anaphylactic properties, the pharmacological screening carried out on the compounds of formula I showed that they are endowed with the property of interfering with the appearance of the allergic pathology experimentally induced in the experimental animal. This

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interference resulted to be remarkable and highly selective.

In the experimental animal, after treatment with the compounds of this invention with even large dosages, no important variations were recorded in the principal regulatory functions studied, such as for example the cardiocirculatory and the respiratory functions.

5 Besides, the coordination functions peculiar to the central nervous system were not influenced and no effect of excitatory or sedative type appeared.

Finally, neither in vitro nor in vivo any direct antagonistic pharmacological action towards humoral and tissue autacoids known in allergic pathology, such as histamine, serotonin, bradykinin and SRS-A was noted.

10 The pharmacological action of the compounds of this invention was shown by a dual series of independent experiments in which:

a) a passive cutaneous anaphylaxis experimental model;

b) an experimental model of systemic sensitization appropriate for the appearance of bronchoconstriction by inhalation of the specific antigen; was induced in the experimental animals.

15 The first test was performed in the rat in accordance with Goose J. and Blair A.M.J.N. [Immunology, 16, 749, (1969)] and Binaghi R.A. and Benacerraf B. [J. Immunol., 92, 920, (1964)]; the production of the hemocytotropic serum necessary for the accomplishment of the test was obtained according to the method set forth by Mota I. [Immunology, 7, 681, (1964)].

The second test was accomplished on guinea-pig, sensitized for 4-5 weeks by parenteral administration of ovalbumin as allergen and adjuvant. The trigger reaction was induced following aerosol inhalation of the allergen until appearance of the characteristic signs of bronchoconstriction.

In these two tests the specific inhibitory activity of the compounds of this invention proved to be dose-dependent and clearly reproducible by the three selected administration ways: oral, peritoneal (i.p.) and venous (i.v.).

25 For example, ED₅₀ value obtained in the passive cutaneous anaphylaxis test in rat is 0.3 mg/kg/i.p. for N-[4-(3-coumarinyl)-2-thiazolyl]oxamate of L-lysine.

In the same experiment known reference compounds gave the following results.

4-phenyl-thiazole oxamic acid

ED₅₀ = 3.5 mg/kg/i.p.

30 4-(4-methoxyphenyl)-thiazole oxamic acid

ED₅₀ = 2.8 mg/kg/i.p.

4-(2-furyl)-thiazole oxamic acid

ED₅₀ = 3.2 mg/kg/i.p.

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Anti-arthritic activity

Anti-arthritic activity was evaluated using the test for Freund experimental arthritis induced in the rat by a subplantar injection of a 0.5% solution of killed *Butyricum mycobacteria* in paraffin oil as described by Newbould B.B. (Brit. J. Pharmacol., 1963, 21, 127).

Compounds found to be active in Freund's experimental arthritis were shown to have considerable clinical usefulness in the treatment of rheumatoid arthritis.

The experimental model of Freund's arthritis used for the pharmacological investigation of the compounds of this invention makes it possible not only to evaluate the pharmacological activity but to acquire indications on the mechanism of the action of the tested compounds.

In this experimental model, in fact, two stages may be considered: the stage sustained predominantly by a specific inflammatory mechanism (primary stage) and the stage sustained principally by an immunity mechanism (secondary stage).

The pharmacological investigation of the compound of this invention was carried out by administering peritoneally to the experimental animal a dosage of 0.06 mmol/Kg/day for a period of 21 consecutive days beginning the day before inoculation of the mycobacteria.

The pharmacological activity was measured by determining both the velocity of erythro sedimentation (VES) and the change in volume of the hind limbs.

The limb which was the seat of the inoculation represents the primary stage while the contra-lateral limb, where the onset of the pathological process takes place about the 12th day after inoculation, represents the secondary stage.

Treatment of the mycobacteria-inoculated animals, for example with N-[4-(3-coumarinyl)-2-thiazolyl]-oxamide led to a 54% inhibition of VES and to a 64% inhibition of volume growth in the contra-lateral limb

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(secondary stage).

The compound known as Cromolyn did not show any anti-arthritis activity in the same test.

Treatment with N-[4-(4-hydroxycoumarin-3-yl)-2-thiazolyl]oxamide led to a 83% inhibition of volume growth in secondary stage.

5 The ratio between pharmacological dose and tolerated dose proved to be highly favourable in all the compounds for the anti-allergic and anti-anaphylactic activity as well as for anti-arthritis activity. Suitable therapeutic doses can be considered between the range from 5 to 500 mg/day depending on the formulation.

10 The therapeutic uses of the compounds of the present invention are in the treatment of the syndromes which accompany the arthritic and rheumatic processes and in the treatment of anaphylaxis reactions and of other various pathological syndromes having a recognized allergic nature, with localization either in the upper respiratory tracts such as, for example, hay fever and bronchial asthma, or in the cutaneous tissues and in superficial mucous membranes such as, for example, urticaria, dermatitis eczematoides, itching and allergic conjunctivitis.

15 Another object of the present invention are the pharmaceutical compositions containing the compounds of formula I or the pharmaceutically acceptable salts thereof as active ingredient.

These compositions can contain the active ingredient together with a pharmaceutically acceptable carrier which may be a solid or liquid, organic or inorganic pharmaceutical excipient and they are suitable for topical, oral, parenteral and rectal administration or for inhalation.

20 The pharmaceutical preparations can be solid, such as for example tablets, pills, capsules, powders, granules, suppositories, or liquid such as for example solutions, suspensions, emulsions, or semiliquids such as creams and ointments.

They can be also prepared in such a way that the release of the drug after administration is prolonged.

25 In addition to the excipients they may contain preservatives, stabilizing agents, wetting agents, emulsifying agents, salts to regulate osmotic pressure, buffers, colouring agents and flavouring agents.

They are prepared according to known methods and can also contain other compatible therapeutic ingredients.

In order to better illustrate the present invention the following examples are now given.

30

Example 1

Preparation of 2-ethoxy-ethyl N-[4-(3-coumarinyl)-2-thiazolyl]oxamate.

35 To a mixture of 2-amino-4-(3-coumarinyl)-thiazole (15.4 g; 63 mmols) and of triethylamine (7.34 g; 72.5 mmols) in pyridine (115 ml), kept under stirring at the temperature of 5°C, 2-ethoxy-ethyl-oxalylchloride (13.1 g; 72.5 mmols) was added dropwise.

40 At the end of the addition, the reaction mixture was kept under stirring for a night at room temperature and, then, was poured onto ice (230 g); it was acidified with concentrated hydrochloric acid and extracted with dichloromethane.

The organic extract was washed with water, dried on sodium sulphate and evaporated.

A solid (24.6 g) was obtained and crystallized from acetonitrile (320 ml) giving 22.9 g (93.5% yield) of the desired compound with m.p. 156-157°C.

45 I.R. (KBr): significant bands at 1730, 1715, 1590, 1540 (cm⁻¹).

Example 2

Preparation of 2-ethoxy-ethyl N-[4-(4-hydroxycoumarin-3-yl)-2-thiazolyl]oxamate.

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To a suspension of 2-amino-4-(4-hydroxycoumarin-3-yl)-thiazole (3.9 g; 15 mmols) in pyridine (40 ml), kept under stirring at the temperature of 5°C, 2-ethoxy-ethyl-oxalylchloride (3.11 g; 17.25 mmols) was added dropwise.

55 At the end of the addition, the reaction mixture was kept under stirring at room temperature for a night and, then, poured into water and ice (80 g). A precipitate formed and it was filtered, suspended in diluted hydrochloric acid, filtered again and washed some times with water till negative halide test.

5.5 g of a solid were obtained and dissolved in dimethylformamide (200 ml) heating (external bath).

After cooling at 0°C the precipitate (4.1 g) was filtered, suspended and kept under stirring in warm

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acetonitrile (100 ml).

After filtration 4 g (65.9% yield) of 2-ethoxyethyl N-[4-(4-hydroxycoumarin-3-yl)-2-thiazolyl]oxamate were obtained with m.p. 266-268°C (dec.).

I.R. (KBr): significant bands at 1735, 1700, 1610, 1555, 1410, (cm⁻¹).

Example 3

Preparation of 2-ethoxyethyl N-[4-(7-hydroxycoumarin-3-yl)-2-thiazolyl]oxamate

To a suspension of 2-amino-4-(7-hydroxycoumarin-3-yl)-thiazole (5.1 g; 19.6 mmols) [p.f. 252-254°C - prepared according to the method described in J. Ann. Chem. Soc. 72, 2993 (1950)] in pyridine (51 ml), kept under stirring at the temperature of 5°C, 2-ethoxy-ethyl-oxalylchloride (8.14 g; 45.1 mmols) was added dropwise.

At the end of the addition, the mixture was kept under stirring at room temperature for a night and, then, poured into water and ice (150 g). It was kept under stirring for 1.5 hours and then the precipitate was filtered.

The solid was suspended in mixture of pyridine (150 ml) and water (50 ml) and the suspension was kept under stirring for 3.5 hours.

After filtration and drying a solid (5.6 g) was obtained and suspended again in warm acetonitrile (100 ml).

By filtration the desired compound (5.1 g; 64.4% yield), crystalline solid with m.p. 217-218°C, was obtained.

I.R. (KBr): significant bands at 1732, 1700, 1610, 1570, 1540, 1380 (cm⁻¹).

Example 4

Preparation of N-[4-(3-coumarinyl)-2-thiazolyl]oxamate of L-lysine dihydrate.

A suspension of 2-ethoxy-ethyl N-[4-(3-coumarinyl)-2-thiazolyl]oxamate (6 g; 15.45 mmols), prepared as described in example 1, in NaOH 0.1N (232 ml) was kept at 40°C under stirring for 45 minutes. The reaction mixture was cooled to room temperature and filtered.

The solid was dissolved in trifluoroacetic acid (40 ml) and re-precipitated with water (200 ml).

The water of crystallization were acidified with hydrochloric acid at 10% till precipitation.

Both the precipitates were filtered together and washed till neutral pH and negative answer to halide test.

After drying 4.8 g of N-[4-(3-coumarinyl)-2-thiazolyl]oxamic acid were obtained and suspended in methanol at 65% (150 ml).

L-lysine (2.44 g; 16.69 mmols) was added and the suspension was heated to boiling temperature till complete solubilization.

By cooling at 0°C a precipitate was obtained and filtered giving 4.6 g (59.7% yield) of the desired compound, crystalline solid with m.p. 203-204°C (dec.).

I.R. (KBr): significant bands at 1715, 1680, 1605, 1540 (cm⁻¹).

Example 5

Preparation of N-[4-(3-coumarinyl)-2-thiazolyl]oxamide.

A suspension of 2-ethoxy-ethyl N-[4-(3-coumarinyl)-2-thiazolyl]oxamate (8 g; 20.6 mmols), prepared as described in example 1, in a solution (115 ml) of ammonia at 16% in methanol was kept under stirring for a night at room temperature.

Then the solvent was evaporated and the solid residue (6.2 g) was crystallized from acetic acid.

5.5 g (84.7% yield) of N-[4-(3-coumarinyl)-2-thiazolyl]oxamide with m.p. 297-300°C were obtained.

I.R. (KBr): significant bands at 1700, 1605, 1545, 1380 (cm⁻¹).

By working in a similar way the following compounds were prepared: N-[4-(4-hydroxycoumarin-3-yl)-2-

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thiazolyl]oxamide, 81.4% yield -p.f. 330°C (dec.).

I.R. (KBr): significant bands at 1680, 1615, 1560, 1410 (cm⁻¹).

N-[4-(7-hydroxycoumarin-3-yl)-2-thiazolyl]oxamide, 73% yield -m.p. 300°C (dec.).

I.R. (KBr): significant bands at 1700, 1610, 1545, 1380 (cm⁻¹).

Example 6

1) Granules containing N-[4-(3-coumarinyl)-2-thiazolyl]oxamate of L-lysine

A mixture of 100 g of active ingredient, 155 g of lactose, 140 g of corn starch and 80 g of crystalline cellulose was stirred and the mixture was kneaded and granulated with a solution of 20 g of hydroxypropyl-cellulose in 400 ml of water and dried at 50°C for 1 hour; then it was passed through a 12 mesh screen to obtain granules which were dried at 50°C for 10 hours.

2) Suppository containing 2-ethoxyethyl N-[4-(3-coumarinyl)-2-thiazolyl]oxamate

A mixture of 5 or 15 g of active ingredient and 180 g of Witepsol (R) W-35 was heated and molten at 60°C and the melt was cast into models so that the weight of each suppository was 1.5 g or 3 g respectively. The cast melt was cooled and solidified to obtain suppositories.

3) Tablets containing N-[4-(4-hydroxycoumarin-3-yl)-2-thiazolyl]oxamide

A mixture of 100 g of active ingredient, 80 g of lactose, 70 g of corn starch and 40 g of crystalline cellulose was granulated in the conventional way.

The granulates was mixed with 4 g of magnesium stearate and formed into tablet each having a weight of 200 mg by a tableting machine.

4) Capsules containing N-[4-(7-hydroxycoumarin-3-yl)-2-thiazolyl]oxamide

A mixture of 100 g of active ingredient, 100 g of lactose, 60 g of corn starch, 40 g of crystalline cellulose and 6 g of magnesium stearate was mixed and filled into hard capsules in an amount of 200 mg for capsule by using an encapsulating machine.

5) Ampoules (injection solution) containing N-[4-(3-coumarinyl)-2-thiazolyl]oxamate of L-lysine

The active ingredient (10 parts by weight), 2 parts by weight of sodium pyrosulfite, 1 part by weight of disodium salt of ethylenediamine-tetraacetic acid, 17 parts by weight of sodium chloride are dissolved in a sufficient quantity of water and brought to 2000 parts by weight with double distilled water. The solution was filtered and filled into 1 ml ampoules and the ampoules were sealed and sterilized.

Each ampoule contains 5 mg of active ingredient.

6) Inhalation Aerosol Preparation containing N-[4-(3-coumarinyl)-2-thiazolyl]oxamide

The active ingredient (1 to 20 parts), soya lecithin (0.20 to 4 parts) and mixture of propellant gases (Freon 11, 12 and 14) up to 100 parts was filled into aerosol containers with metering valve. The single dose can be adjusted to provide 1 to 20 mg of active substance.

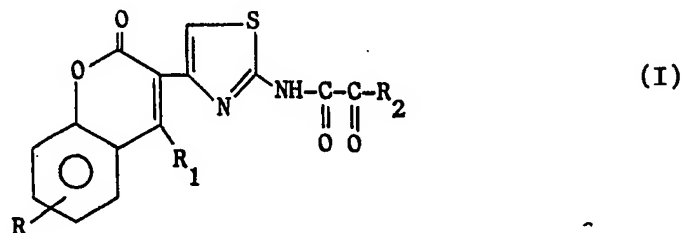
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Claims

1) A compound of formula

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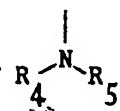
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wherein

R and R₁ represent hydroxy, a hydrogen or a halogen atom, a C₁-C₄ alkyl or alkoxy;

R₂ represents hydroxy, an OR₃ group or a

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group;

R₂ represents a C₁-C₄ alkyl, a benzyl, a group of formula -(CH₂-CH₂-O)_n-R₆, wherein n represents an integer from 1 to 4 and R₆ represents a hydrogen atom or a C₁-C₄ alkyl;

R₄ and R₅, which are the same or different, represent a hydrogen atom, a C₁-C₄ alkyl, a benzyl, a phenyl, or R₄ and R₅ together with the nitrogen atom to which they are bonded, form a 1-piperidinyl, 1-piperazinyl, 4-

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methyl-1-piperazinyl radical;

and salts thereof with pharmaceutically acceptable acids or bases.

2) A compound, according to claim 1, wherein R and R₁ represent a hydrogen, a chlorine or bromine atom, hydroxy, a methoxy or ethoxy group.

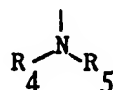
3) A compound according to claim 1, wherein R₂ represents an OR₃ group.

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4. A compound according to claim 1, wherein R₂ represents hydroxy and salts thereof with non-toxic organic or inorganic bases suitable for pharmaceutical use.

5. A compound according to claim 1, wherein R₂ represents a

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group.

6) A compound according to claim 1, wherein R₄ and R₅, the same or different, represent hydrogen, methyl or ethyl or together with the nitrogen atom to which they are bonded form a 1-piperidinyl, 1-piperazinyl or 4-methyl-1-piperazinyl radical.

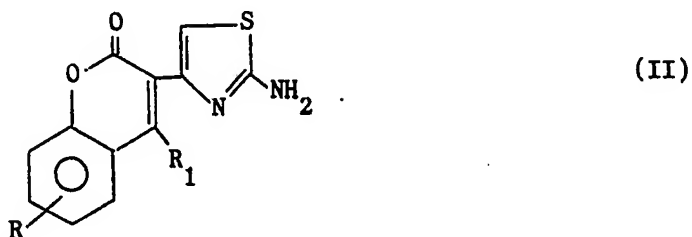
7) A process for the preparation of the compounds of formula I comprising to react a compound of

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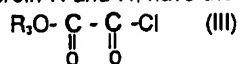
formula

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wherein R and R₁ have the meanings reported in claim 1, with a compound of formula



wherein R₂ has the meanings reported in claim 1, in the presence of an organic or inorganic base and of a solvent that may be the organic base itself, in order to obtain the compounds of formula I wherein R₂ = OR₃; from these, optionally, by hydrolysis or by reaction with ammonia or with an amine the other compounds of formula I are obtained.

8) A pharmaceutical composition containing an effective amount of a compound according to claim 1, together with a pharmaceutically acceptable carrier.

9) A pharmaceutical composition according to claim 8, for the treatment of allergic and anaphylactic diseases containing a therapeutically effective amount of a compound according to claim 1, with a pharmaceutically acceptable carrier.

10) A pharmaceutical composition according to claim 8, for the treatment of arthritis containing a therapeutically effective amount of a compound according to claim 1, with a pharmaceutically acceptable carrier.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 10 4557

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D,A	GB-A-2 023 580 (BOEHRINGER INGELHEIM GMBH) * claims 1,8,11; abstract; page 2, lines 27-62; page 3, lines 4-7; page 4, table *	1,7-10	C 07 D 417/04 A 61 K 31/425
D,A	EP-A-0 044 442 (BASF AG) * claims 1,5,7; abstract *	1,7-10	
A	WO-A-8 600 899 (ZAMBON, S.P.A.) * claims 1,7,8,10; page 3, lines 5-24 *	1,7-10	
A	WO-A-8 600 900 (ZAMBON, S.P.A.) * claims 1,6,10; abstract *	1,7-10	
A	EP-A-0 006 368 (PIERRE FABRE S.A.) * claims; abstract *	1,7-10	
A	EP-A-0 052 564 (PIERRE FABRE S.A.) * claims; abstract *	1,7-10	
A	CHEMICAL ABSTRACTS, vol. 105, no. 25, 22nd December 1986, page 16, abstract no. 218302h, Columbus, Ohio, US; H. COUSSE et al.: "Studies of arylthiazole oxamates in relation to oral antiallergic activity", & ARZNEIM.-FORSCH. 1986, 36(9), 1391-1393	1,8-10	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 417/00
A	CHEMICAL ABSTRACTS, vol. 99, no. 17, 24th October 1983, page 599, abstract no. 139932t, Columbus, Ohio, US; & JP - A - 58 35186 (MITSUI TOATSU CHEMICALS, INC.) 01-03-1983	1,8-10	
		-/-	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 20-06-1988	Examiner HASS C V F
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			



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EUROPEAN SEARCH REPORT

Page 2

Application Number

EP 88 10 4557

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 99, no. 21, 21st November 1983, page 613, abstract no. 175646m, Columbus, Ohio, US; A. GURSOY et al.: "Some derivatives of coumarinythiazolylamide and urethane. II.", & DOGA, SERI C 1983, 7(2), 137-145 ---	1	
A	THE MERCK INDEX "Crotethamide", 9th edition, 1976, page 337, no. 2585, Rahway, New Jersey, US; -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 20-06-1988	Examiner HASS C V F
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	